REMARKS/ARGUMENTS

Claims 1, 3-14, 25-35, and 70-71 have been examined. Claims 1 and 25 have been amended. No new matter has been added by the amendments as discussed herein below. For convenience, the Examiner's rejections are addressed in the order presented in the February 3, 2009, Office Action. Applicants respectfully request reconsideration of the pending claims in light of the above amendments and the below remarks.

I. Status of the claims

Claims 1 and 25 are amended to recite that only a colorectal mucosal tissue of the subject is contacted with the immunogenic peptide as the means of producing an effective immune response. No additional subject tissue is contacted to induce the antigen specific systemic and colorectal mucosal cytotoxic T lymphocyte (CTL) response. Support for this amendment is found throughout the specification, for example, at page 33, lines 33-35; page 34, lines 13-15 and lines 29-33; page 35, lines 20-23; page 36, lines 1-9 and lines 33-35; page 37, lines 11-14 and lines 23-25; page 38, lines 3-9; page 39, lines 21-27. Support for colorectal administration is found throughout the specification, for example, at page 5, line 37 through page 6, line 1 and at page 21, lines 17-21. These amendments add no new matter.

II. Rejections under 35 U.S.C. §103(a)

Claims 1, 3, 4, and 25 remain rejected as allegedly obvious over various combinations of references. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. Recently, in

reviewing this standard, the Supreme Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR Intl Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

While the Court warned against a "rigid application" of the TSM test, the Court also found that these questions could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a). *Id.* at 1396-1397. *See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007.

A. Klavinskis et al., and Ahlers et al. or Berzofsky et al.

Claims 1, 3, 4, and 25 remain rejected as allegedly obvious over Klavinskis *et al.* (*J. Immunol.* 157:2521-2527 (1996)) and either Ahlers *et al.*, (*J. Immunol.* 158:3947-3958 (1997)) or Berzofsky *et al.*, (WO 94/26785). According to the Office Action, Klaviskis *et al.*, discloses rectal and vaginal immunization by administering an SIV peptide antigen linked to a cholera toxin subunit. This immunization schedule allegedly resulted in cytotoxic T lymphocytes (CTLs) that could be isolated from the rectal mucosa and that were antigen specific. Ahlers *et al.* and Berzofsky *et al.* allegedly disclose the recited antigenic sequence, SEQ ID NO:9. According to the Office Action, one of skill would have been motivated to practice the claimed invention by a suggestion of Klavinskis *et al.* that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTLs in the rectal or genital tract. Office Action at page 3 bridging to page 4. In addition, the Examiner has alleged that given that there is a recognized need in the art to raise a mucosal immune response at the site of transmission, it would have been obvious to administer an antigen/construct to the rectal mucosa in order to reduce transmission. The Examiner has also alleged that there would have been a

reasonable expectation of success given the findings of Klavinskis *et al.* that mucosal or targeted lymph node immunization generates antigen-specific CTL in the rectal and genital mucosa.

The Examiner has considered Applicants prior response and not found it persuasive. In particular, the Examiner has summarized Applicants' response as arguing that the claimed invention is directed to administering antigen to only colorectal tissue; whereas Klavinskis *et al.* disclose rectal or vaginal administration followed by three oral administrations of the vaccine. In response the Examiner alleges that in Klavinskis *et al.* at the time of administering the antigen to mucosal tissue, rectal or colorectal mucosal tissue was the only site of administration and that the oral administrations were carried out months after the rectal administration. The Examiner does not believe that the pending claims eliminate further antigen administration at a later time in the future via another route or the same route. The Examiner further believes that the new limitations to the pending claims merely describes what happens at a particular point in time, *i.e.*, at first exposure to the antigen, but does not address what may happen later.

Applicants respectfully disagree. The claimed method is immunization of a subject by administering SEQ ID NO:9 using only a colorectal tissue as the site of administration of the composition. In contrast, Klavinskis *et al.* disclose only a combination immunization schedule that results in the induction of antigen specific cytotoxic T cells. That is, Klavinskis *et al.* teach administration at a rectal or vaginal site, followed by three oral administrations of the vaccine results in the induction of antigen-specific CTL. There is no disclosure or suggestion that only colorectal or vaginal administration of the composition of Klavinskis *et al.* resulted in any systemic or colorectal mucosal immune response. Klavinskis *et al.* therefore provide no suggestion or motivation to reduce or eliminate the oral administration of the vaccine so as to induce the same or similar immune response that includes an antigen specific CTL response in both the systemic and rectal mucosa. As such, there can be no reasonable expectation of success whether the administration of an antigen to strictly and only rectal mucosa would induce such an immune response. The previously provided declaration from Dr. Jay Berzofsky fully reviews the disclosure of Klavinskis *et al.* and first states that the claimed peptide (SEQ ID NO:9) and the

peptide exemplified in the specification (Seq ID NO:2) share the identical immunogenic helper peptide sequence and slightly different variations of the same immunogenic CTL epitope sequence. Thus, Dr. Berzofsky believes that similar immune responses would be generated by both peptides. Further, Dr. Berzofsky states that on reading Klavinskis *et al.*, in his opinion, a skilled artisan would understand that the three additional oral administrations of antigen were **required** to raise an immune response against the antigen. Thus, Klavinskis *et al.* teach away from the claimed invention, which requires administration of antigen only to a colorectal site. The other cited references, Ahlers *et al.* and Berzofsky *et al.*, do not disclose colorectal administration of an HIV antigen. Therefore, the claimed invention is not obvious in view of the cited references.

Further, although Applicants fully believe that claims 1 and 25 limit the administration of the peptide to only colorectal mucosa and do not encompass administration by any systemic means, claims 1 and 25 have been amended to set forth the region of administration with greater particularity. Specifically, claims 1 and 25 have been amended to recite "contacting only a colorectal mucosal tissue of the subject" with the peptide depicted as SEQ ID NO: 9. Applicants believe that such amendment limits the administration of the peptide to only colorectal mucosal tissue and does not encompass any administration of the peptide to lymph nodes or other systemic administration.

B. Klavinskis et al., and Ahlers et al. or Berzofsky et al., in further view of Kiyono et al.

Claims 1, 5-14, and 25-35 remain rejected as allegedly obvious over Klavinskis *et al.* and either Ahlers *et al.* or Berzofsky *et al.*, as applied to claims 1, 3, 4, and 15 above and in further view of Kiyono *et al.* (*Advanced Drug Delivery Reviews* 18:23-51 (1995)). According to the Office Action, Ahlers *et al.* teach immunizing a subject with the peptide of SEQ ID NO:9 and various cytokines and that it was found that GM-CSF synergized with IL-12 for CTL induction. Kiyono *et al.* allegedly provides motivation to do so by suggesting that Th cell-

derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses. Office Action at page 6.

The Examiner has considered Applicants' prior argument and considers that argument non-persuasive. In particular, the Examiner alleges that cytokines, like the antigen being administered are proteins, and that it is not clear how Applicants, or one of skill in the art, would expect the protein antigen to survive in the colon and maintain its function (*e.g.*, successfully immunize the subject). Further, the Examiner alleges that to the contrary, based on the teachings of Klavinskis *et al*, protein antigens can be administered rectally to a subject and result in some degree of protection and CTL induction. As such, the Examiner concludes that "it seems reasonable to believe that a cytokine, which is also a protein, could also be administered with the expectation of enhancing the immune response".

Applicants must again respectfully disagree with the rejection of the Examiner. Ahlers *et al.* and Berzofsky *et al.* disclose only systemic administration of antigen. Kiyono *et al.* disclose various approaches to vaccination with DNA, virus vectors, and other non-peptide constructs. Kiyono *et al.* also make a brief statement about Th-cell derived cytokines and the balance of Th1 and Th2 cell responses. There is no disclosure or suggestion relating to administered cytokines, much less non-Th-cell derived cytokines. Claims 6, 27, and 71, recite administration of a cytokine to a colorectal mucosal surface. The specification demonstrates that colorectal administration of IL-12, a non-Th-cell derived cytokine, with SEQ ID NO:2 provides a significant increase in CTL level in both mucosal and systemic sites as compared to colorectal administration of SEQ ID NO:2 without IL-12. *See, e.g.*, specification at page 36, lines 1-9. In addition, intraperitoneal (IP) treatment with IL-12 combined with the colorectal immunization of SEQ ID NO:2 did not increase CTL levels. *See. e.g.*, specification at Example 11, page 45 and Figure 15. As above, according to Dr. Berzofsky, similar immune responses are raised by SEQ ID NO:2 and the claimed SEQ ID NO:9.

In his declaration, Dr. Berzofsky states that the activity of a cytokine after administration to a colorectal mucosal surface was surprising. Unlike subcutaneous administration, colorectal administration requires the cytokine to retain activity after passing

through the hostile environment of the colon. To maintain activity, a cytokine protein must maintain a specific, active structure to allow binding to a cytokine receptor on an appropriate cell. An active cytokine protein requires some minimum of the amino acid sequence to be present in a tertiary structure that is recognized by an appropriate cytokine receptor. According to Dr. Berzofsky, the colon is colonized by bacteria and contains bacterial proteases that can degrade the amino acid sequence of proteins, including cytokines. Thus, according to Dr. Berzofsky, one of skill would not expect the administered cytokine to be active after administration to the colon. In addition, Dr. Berzofsky states that, in order to reach cells that express a cytokine receptor, the cytokine had to pass from the colorectal space and through a protective layer of mucus. The passage of the cytokine through the mucus layer and maintenance of activity would not have been expected by those of skill in Dr. Berzofsky's opinion.

Further, the Examiner is not correct that a cytokine and a protein or peptide antigen are equivalent and must remain fully intact in order to induce an immune response. It is well known to the skilled artisan that a protein antigen does not have to be intact, but can induce an immune response even if cleaved by proteases into peptide fragments. It is well known that certain peptide fragments can bind to MHC molecules. In contrast, as above, a cytokine must remain sufficiently intact and/or uncleaved to retain its ability to bind to its receptor and maintain cytokine activity. As such, a cytokine is much more at risk of being inactivated by proteases in the colorectal milieu than is the antigen itself.

In view of the above amendments and remarks, reconsideration of the rejection and withdrawal of the rejection for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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